REMARKS

Amendments in the claims

Claims 16, 17 and 24–78 are now pending in the present application, of which Claims 16, 36 and 68–77 are presently withdrawn from consideration. Claims 18–23 are canceled and Claim 78 added by the present amendment. No increase in total number of claims or in number of independent claims results from this amendment and no additional claim fees are believed payable.

Claim 17 is amended without prejudice to focus the present application on an embodiment of the invention wherein the agent administered according to the claimed method is 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol or a physiologically acceptable salt thereof. This species was formerly the subject of now-canceled Claim 23. This amendment is requested in the interest of advancing prosecution by reducing the number of issues in examination. No admission is made that the claim as previously presented, reciting an art-recognized genus of compounds, is not patentable, and Applicant reserves the right to reintroduce presently canceled subject matter in a later filed continuation application.

Claim 17 is further amended to delete the phrase "or a racemate or pure (R)- or (S)-enantiomer thereof". As the chemical name "5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl] amino]-1-naphthol" embraces as subspecies thereof the pure (R)-enantiomer, the pure (S)-enantiomer and the racemate, no change in claim scope results from this deletion. Applicant believes that greater clarity results from recitation of these subspecies in a separate dependent claim (new Claim 78, added by the present amendment).

Following amendment herein, Claim 17 still reads on the presently elected species.

Cancellation of Claims 18–23 is requested without prejudice, and is necessitated by amendment of Claim 17 herein.

Claims 30–34, 51–55, 66 and 67 are amended in alignment with Claim 17 from which they directly or ultimately depend, to retain proper antecedent basis.

Claims 37 and 57 are amended as to dependency. Claim 37 is further amended for consistency in naming the (S)-enantiomer.

New Claim 78 reads on the presently elected species, rotigotine, which is the (S)-enantiomer of 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl] amino]-1-naphthol.

No new matter is added, and no change in inventorship is believed to result from the present amendment.

RESPONSE TO OFFICE ACTION DATED 7 APRIL 2009

1. Initial comments

The present Action recognizes the claim of priority and acknowledges the properly filed Information Disclosure Statement.

Applicant acknowledges withdrawal of the requirement for restriction among Groups II–VI and for election of species of depression and affective disorders (Action, p. 2 and pp. 3–4 respectively). Although there is some ambiguity in the Action, Applicant understands the Action to make final the restriction between, on the one hand, Claim 16 and claims depending therefrom, and on the other hand, Claim 17 and claims depending therefrom, such that Claims 17–35 and 37–67 have been examined on the merits. If this understanding is incorrect, Applicant requests clarification in the next action.

2. Non-statutory double patenting

Claims 17–35 and 37–67 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly unpatentable over Claims 10–82 of copending application Serial No. 10/565,699 ("the '699 application").

First, Applicant notes that presently amended Claim 17 is directed to a method of treating depression in a mammal by administering to the mammal a therapeutically effective amount of 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol or a physiologically acceptable salt thereof. Claim 17 is not limited to a "method of treating depression comprising administering compounds including rotigotine (elected species) and additional drugs that include antidepressants, antipsychotics, anxiolytics, anti-migraine [agents] and sedatives" as implied in the Action (p. 5).

Second, the rejection is provisional because the allegedly conflicting claims have not yet been patented. Applicant may elect to argue to overcome this ground of rejection or to provide a terminal disclaimer (to the extent necessary) once the present claims have been found to be otherwise allowable and/or once the '699 application issues as a patent.

3. Rejection under 35 U.S.C. §112, first paragraph

Claims 17–35 and 37–67 stand rejected under 35 U.S.C. §112, first paragraph as allegedly failing to meet the enablement requirement of that paragraph. This rejection is moot with respect to now canceled Claims 18–23 and is respectfully traversed with respect to Claims 24–35 and 37–67.

The Action (p. 6) asserts that the specification "while demonstrating the suitability of rotigotine as an antidepressant in three animal models ... does not reasonably provide enablement for treating depression with any other compounds listed in [the] formula of Claim 17." Following amendment herein to focus Claim 17 on 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol or a salt thereof as the compound administered, Applicant submits that the data for treatment of depression with rotigotine (the (S)-enantiomer of 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol) are enabling for the full scope of Claim 17.

The Action also states (p. 6) that "the specification does not reasonably provide enablement for treating depression in a combination therapy as claimed (Claims 35, 58–66) with addition of one or more antid[e]pressants, anxiolytics, sedatives, antipsychotics and anti-migraine agents."

Applicant agrees with the Action (p. 7) that the "relative skill of those in the pharmaceutical and medical arts is high, requiring advanced education and training." Applicant also agrees with the Action (p. 7) that "the art is highly unpredictable." However, with respect to the statements that "[i]t is still not possible to predict the pharmacological activity or treatment efficacy of a compound based on structure alone", and that "[i]t is impossible to predict whether the compound or class of compounds based on the chemical structure ... would actually be effective for treating depression", Applicant respectfully points out that:

- antidepressive effect of 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol is taught in the present specification; and
- the classes of agent used in combination with 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol according to Claims 35 and 58–66 are known in

the art to be useful in treatment of depression or related or associated disorders.

At paragraph **[0056]**, the specification as filed teaches that "[d]epending on the cause and the symptoms of the depression, a combination preparation may also contain an additional antipsychotic, sedative, anxiolytic, or anti-migraine agent, or an active ingredient which displays one or more effects selected from an antidepressive, antipsychotic, sedative, anxiolytic or anti-migraine effect" (emphasis added). The Action (p. 17) states that "[i]t is well within the [art of the] skilled medical professional to determine suitable dosing regimens." It follows from this admission and from the present disclosure that enablement exists for one of skill in the art to treat depression by administering a therapeutically effective amount of 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol in combination with one or more additional active ingredients having an antidepressive, antipsychotic, sedative, anxiolytic or anti-migraine effect.

Withdrawal of the present rejection under 35 U.S.C. § 112, first paragraph is respectfully requested.

4. Rejection under 35 U.S.C. §103(a) over Van der Weide, Andersson and Sherman in view of Lauterbach

Claims 17–34 and 37–54 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Van der Weide *et al.* (1988) Eur. J. Pharmacol. 146:319–326 ("Van der Weide"), European Patent Publication No. 0 334 538 ("Andersson") and Sherman (2001) Clinical Psychiatry News, Nov. 1, 2001 ("Sherman") in view of International Publication No. WO 02/089777 ("Lauterbach"). This rejection is respectfully traversed.

Even if a rationale existed to select and modify elements from the cited documents (which is not admitted herein), the Examiner appears to be applying the "obvious to try" standard in making the present rejection. This standard has been sanctioned by *KSR International Co. v. Teleflex Inc.,* 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), but with the proviso that there has to be "a finite number of identified, predictable solutions" (emphasis added). Furthermore, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* (emphasis added). As paraphrased in MPEP 2143.01(III), "[t]he mere fact that references can be

combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art."

At the time of the present invention, it could not have been predicted that 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol would be effective in treatment of depression in a mammal. Andersson sets forth particular 1,2,3,4-tetrahydro-2-naphthyl-amines. The Action (p. 14) admits that "Andersson does not teach the claimed compounds" but asserts that "the compounds of Andersson are structurally similar to compounds of claim 1 [*sic*, 17]." Sherman reports on pramipexole, not 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol. As the Examiner admits (Action, p. 7), "[d]espite the advance training to those in the art, the art is highly unpredictable. It is still not possible to predict the pharmacological activity or treatment efficacy of a compound based on the structure alone…[and i]t is impossible to predict whether the compound or class of compounds based on the chemical structure that they would actually be effective for treating depression." This position is supported by the recent Federal Circuit decision in *Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989 (Fed. Cir. 2009). In that case, U.S. Patent No. 4,761,406 ("the '406 patent") relates to an intermittent dosing method whereby any of 36 specified bisphosphonates, one of which is the compound 2-pyr EHDP, can be used in treatment of osteoporosis without the unwanted side effect of anti-mineralization. The court held that the '406 patent did not render the claims of U.S. Patent No. 5,583,122, reciting the compound risedronate, obvious, despite risedronate and 2-pyr EHDP being positional isomers.

Accordingly, even if, *arguendo,* the compounds of Andersson and Sherman are similar to the presently recited 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol, neither Andersson nor Sherman, nor a combination thereof, renders instant Claim 17 obvious. Since the art is admittedly "so highly unpredictable", one of ordinary skill in the art would not predict therapeutic effectiveness of 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol in depression just from disclosure of structurally "similar" compounds by Andersson and Sherman.

(Although the point is moot in view of amendment of Claim 17 herein, Applicant respectfully draws attention to an error in the structure of Applicant's compounds shown at p.

13 of the Action, wherein R1 and R5 are interchanged.)

Van der Weide states that (+)N-0437 (rotigotine) "could have a possible therapeutic application in schizophrenia". This speculative comment, even if combinable with the disclosures of Andersson and Sherman, fails to suggest any predictability of outcome of treating depression with rotigotine. This deficiency is not corrected by combination with Lauterbach, relating to a method of treating Parkinson's Disease using a transdermal therapeutic system delivering rotigotine.

As the Examiner (Action, p. 7) admits, "in order to verify that a compound will be effective in treating a disease [in this case depression], the [compound] must be ... tested directly in a patient or in a model that has been established as being predictive of ... efficacy" in treatment of depression. Absent such testing, one of ordinary skill in the art at the time of the present invention cannot have had a reasonable expectation of success, *i.e.*, could not reasonably have predicted the therapeutic effectiveness of 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol or salts thereof in treating depression.

The antidepressant action of 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol was first demonstrated by the present inventors, using three different, validated animal models, as set forth in the specification as filed, at paragraphs **[0015]–[0019]**. In the "forced swim test" (specification, Fig. 1), rotigotine led to a clear reduction in the period of immobility. In the "learned helplessness test", rotigotine at low doses improved learning behaviour (specification, Fig. 2). Finally, in bulbectomized rats, low doses of rotigotine reduced motor hyperactivity in a fashion similar to the antidepressant imipramine (specification, Fig. 3). It is only with testing such as this, first conducted by the present inventors, that any predictability of antidepressant activity of 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol or salts thereof became possible. As the results of treatment by the method of Claim 17 were <u>not</u> predictable from the cited art, the "obvious-to-try" standard is not sufficient under *KSR, supra* to sustain a *prima facie* case of obviousness.

Notwithstanding the Examiner's comments with regard to specific dependent claims, each of Claims 18–34 and 37–54 is nonobvious over Van der Weide, Andersson and Sherman in view of Lauterbach for at least the same reasons that Claim 17 is nonobvious.

It is noted that Claim 55 has not been made subject to the present rejection. If this is

merely an oversight on the part of the Examiner, Applicant submits that the arguments for nonobviousness of Claims 17–34 and 37–54 above apply *mutatis mutandis* to Claim 55.

Withdrawal of the present rejection under 35 U.S.C. §103(a) over Van der Weide, Andersson and Sherman in view of Lauterbach is respectfully requested.

5. Rejection under 35 U.S.C. §103(a) over Van der Weide, Andersson and Sherman in view of Lauterbach and Maj

Claims 35, 56, 57, 66 and 67 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Van der Weide, Andersson and Sherman in view of Lauterbach and further in view of U.S. Patent No. 6,255,329 ("Maj"). This rejection is respectfully traversed.

Claims 35, 56, 57, 66, and 67 depend from Claim 17 and are drawn to a method of Claim 17 that further includes administering to the mammal an additional active ingredient such as an antidepressant. For the reasons set forth above, a *prima facie* case of obviousness of Claim 17 (and thus of any claim dependent therefrom) over Van der Weide, Andersson and Sherman in view of Lauterbach is not sustainable. Addition of Maj to the combination of documents does not change this conclusion. Maj is cited for disclosure of a combination of pramipexole and sertraline. Even if, *arguendo*, such disclosure, combined with the other cited art, were to suggest to one of skill in the art a combination of compounds with known antidepressant activity, the fact remains that 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol was not known to have such activity prior to the present invention, therefore the cited art fails to teach or suggest the invention as claimed in Claims 35, 56, 57, 66 and 67.

Withdrawal of the present 35 U.S.C. §103(a) rejection over Van der Weide, Andersson and Sherman in view of Lauterbach and further in view of Maj is respectfully requested.

6. Rejection under 35 U.S.C. §103(a) over Van der Weide, Andersson and Sherman in view of Lauterbach and Hrdlička

Claims 58 and 59 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Van der Weide, Andersson and Sherman in view of Lauterbach and further in view of Hrdlička (2002) Eur. Psychiatry 17:484 ("Hrdlička"). This rejection is respectfully traversed.

Claims 58 and 59 depend from Claim 17 and are drawn to a method of Claim 17 that

further includes administering to the mammal an additional active ingredient that is an antipsychotic. For the reasons set forth above, a *prima facie* case of obviousness of Claim 17 (and thus of any claim dependent therefrom) over Van der Weide, Andersson and Sherman in view of Lauterbach is not sustainable. Addition of Hrdlička to the combination of documents does not change this conclusion. Hrdlička is cited for disclosure of a one-patient study of a combination of clozapine and maprotiline. Even if, *arguendo*, such disclosure, combined with the other cited art, were to suggest to one of skill in the art a combination of a compound with known antidepressant activity and an antipsychotic, the fact remains that 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol was not known to have antidepressant activity prior to the present invention, therefore the cited art fails to teach or suggest the invention as claimed in Claims 58 and 59. The Action mentions Timmerman *et al.* (1990) Eur. J. Pharmacol. 181:253–260 as remarking that "(+)N-0437 is a possible candidate for therapeutic use in schizophrenia"; however, this document does not appear to be applied in the present rejection and the recited disclosure appears in any case to be merely cumulative over that of Van der Weide.

Withdrawal of the present 35 U.S.C. §103(a) rejection over Van der Weide, Andersson and Sherman in view of Lauterbach and further in view of Hrdlička is respectfully requested.

7. Rejection under 35 U.S.C. §103(a) over Van der Weide, Andersson and Sherman in view of Lauterbach and Kupfer

Claims 60 and 61 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Van der Weide, Andersson and Sherman in view of Lauterbach and further in view of Kupfer (1999) Ann. Clin. Psychiatry 11:267–276 ("Kupfer"). This rejection is respectfully traversed.

Claims 60 and 61 depend from Claim 17 and are drawn to a method of Claim 17 that further includes administering to the mammal an additional active ingredient that is a sedative. For the reasons set forth above, a *prima facie* case of obviousness of Claim 17 (and thus of any claim dependent therefrom) over Van der Weide, Andersson and Sherman in view of Lauterbach is not sustainable. Addition of Kupfer to the combination of documents does not change this conclusion. Kupfer is cited for the disclosure that depression can be accompanied by insomnia. The Action mentions U.S. Patent Application Publication No.

2002/0177626 as disclosing that diphenhydramine is a sedative, though this document does not appear to be applied in the present rejection. Even if, *arguendo*, the disclosure of Kupfer, combined with the other cited art, were to suggest to one of skill in the art a combination of a compound with known antidepressant activity and a sedative, the fact remains that 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol was not known to have antidepressant activity prior to the present invention, therefore the cited art fails to teach or suggest the invention as claimed in Claims 60 and 61.

Withdrawal of the present 35 U.S.C. §103(a) rejection over Van der Weide, Andersson and Sherman in view of Lauterbach and further in view of Kupfer is respectfully requested.

8. Rejection under 35 U.S.C. §103(a) over Van der Weide, Andersson and Sherman in view of Lauterbach and Zimmerman

Claims 62 and 63 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Van der Weide, Andersson and Sherman in view of Lauterbach and further in view of Zimmerman & Chelminski (2003) Am. J. Psychiatry 160:504–512 ("Zimmerman"). This rejection is respectfully traversed.

Claims 62 and 63 depend from Claim 17 and are drawn to a method of Claim 17 that further includes administering to the mammal an additional active ingredient that is an anxiolytic. For the reasons set forth above, a *prima facie* case of obviousness of Claim 17 (and thus of any claim dependent therefrom) over Van der Weide, Andersson and Sherman in view of Lauterbach is not sustainable. Addition of Zimmerman to the combination of documents does not change this conclusion. Zimmerman is cited for the disclosure that depression can be accompanied by generalized anxiety disorder (GAD). The Action mentions Lehmann (1989) Neuropsychobiology 21:197–204 as disclosing that fluspirilene is an anxiolytic, though this document does not appear to be applied in the present rejection. Even if, *arguendo*, the disclosure of Zimmerman, combined with the other cited art, were to suggest to one of skill in the art a combination of a compound with known antidepressant activity and an anxiolytic, the fact remains that 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol was not known to have antidepressant activity prior to the present invention, therefore the cited art fails to teach or suggest the invention as claimed in Claims 62 and 63.

Withdrawal of the present 35 U.S.C. §103(a) rejection over Van der Weide, Andersson

and Sherman in view of Lauterbach and further in view of Zimmerman is respectfully requested.

9. Rejection under 35 U.S.C. §103(a) over Van der Weide, Andersson and Sherman in view of Lauterbach and Medicine News

Claims 64 and 65 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Van der Weide, Andersson and Sherman in view of Lauterbach and further in view of Anon. (2003) "Links between depression and migraine" www.bio-medicine.org/medicine-news/Links-between-Depression-and-Migraine-2005-1/ ("Medicine News"). This rejection is respectfully traversed.

Claims 64 and 65 depend from Claim 17 and are drawn to a method of Claim 17 that further includes administering to the mammal an additional active ingredient that is an anti-migraine agent. For the reasons set forth above, a *prima facie* case of obviousness of Claim 17 (and thus of any claim dependent therefrom) over Van der Weide, Andersson and Sherman in view of Lauterbach is not sustainable. Addition of Medicine News to the combination of documents does not change this conclusion. Medicine News is cited for the disclosure that treatments for migraine and major depression can benefit patients with both disorders. The Action mentions U.S. Patent Application Publication No. 2003/0225002 as disclosing that almotriptan is an anti-migraine agent, though this document does not appear to be applied in the present rejection. Even if, *arguendo*, the disclosure of Medicine News, combined with the other cited art, were to suggest to one of skill in the art a combination of a compound with known antidepressant activity and an anti-migraine agent, the fact remains that 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol was not known to have antidepressant activity prior to the present invention, therefore the cited art fails to teach or suggest the invention as claimed in Claims 64 and 65.

Withdrawal of the present 35 U.S.C. §103(a) rejection over Van der Weide, Andersson and Sherman in view of Lauterbach and further in view of Zimmerman is respectfully requested.

10. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed,

accommodated, or rendered moot herein. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the application is in condition for allowance.

If personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number below.

Respectfully submitted,

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